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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/543,048	01/26/2006	Philipp Hadwiger	A2038-7052US	3878

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LOWRIE, LANDO & ANASTASI, LLP
A2038
ONE MAIN STREET, SUITE 1100
CAMBRIDGE, MA 02142

EXAMINER	
CHONG, KIMBERLY	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
05/12/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/543,048	HADWIGER ET AL.	
	Examiner	Art Unit	
	KIMBERLY CHONG	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *86,89,90,94-98,100-102 and 110-119* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *86,89,90,94-98,100-102 and 110-119* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 02/22/2008 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 08/22/2007 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 08/22/2007, claims 86, 89, 90, 94-98, 100-102, and 110-119 are pending in the application. Applicant has canceled claims 1-85, 87-88, 91-93, 99 and 103-109.

Response to Applicant's Arguments

Re: Claim Rejections - 35 USC § 112

Rejection of claims 117 and 119 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is moot in view of the claim amendments filed 02/22/2008.

Re: Claim Rejections - 35 USC § 103

The rejection of claims 86, 89, 90, 94-98, 100-102, 110-119 under 35 U.S.C. 103(a) as being unpatentable over Rana, T. (US 2005/0020521) in view of Florence et al. (Journal of Controlled Release, 2000, Vol. 65: 253-259), Manoharan, M.

(20030064492, "Manoharan I") and Cook et al. (U.S. Patent No. 6,803,198) and evidenced by Manoharan, M. (Applicant's IDS 02/13/2006, "Manoharan II") is maintained for the reasons of record in the Office action mailed 08/22/2007.

Applicant's arguments filed 02/22/2008 have been fully considered but they are not persuasive. Applicant argues that the references, both alone and when read in combination would not render obvious the claimed invention. Specifically, Applicant argues Rana suggests any modification of the ends of the RNA and do not teach the claimed invention of only one lipophilic group in a specific location on the RNA molecule. Applicant argues that while Florence et al. does teach the use of lipophilic groups such as dendrimers, Florence et al. does not teach the claimed invention "i.e. the use of only one lipophilic group attached at a specific portion of an RNA strand" and Florence et al. do not teach the dendrimer associated with any drug or molecule or show any covalent linking point and further Florence et al. does not provide any guidance as to how to covalently link the dendrimer to the molecule.

Applicant's arguments are not convincing. Because Rana teach modifications of dsRNA at the 3' or 5' ends of either strand and the modifications can comprise dendrimers, it would have been obvious to one of ordinary skill in the art to use the dendrimers taught by Florence et al. for attachment to a RNA strand, specifically at the 3' and 5' ends as taught by Rana, particularly given Florence et al. teach such dendrimers are efficient drug delivery vehicles for molecules.

Applicant further argues Florence et al. do not teach $\log K_{ow}$ is an essential characteristic of delivery of the dendrimer and makes no connection between the $\log K_{ow}$

exceeding 1 and the delivery potential of the dendrimer. Applicant further states the Florence et al. states there is an optimum size for nanoparticle uptake and the repeated reference to an optimal size would not have led one skilled in the art to use dendrimers with $\log K_{ow}$ exceeding 1. Applicant's arguments are not convincing. The instant claims are drawn to a dsRNA comprising a sense and antisense strand and one lipophilic group having a $\log K_{ow}$ exceeding 1 and do not recite the $\log K_{ow}$ of the lipophilic group being an essential characteristic of the conjugate. Further, Florence et al. teach synthesis of a dendrimer wherein the dendrimer has a $\log K_{ow}$ of 17.5 and teach this particular dendrimer efficiently translocated across cell layers. Therefore, one of ordinary skill in the art would have used a dendrimer with the same characteristics given Florence et al. teach such dendrimer can efficiently be used as a drug delivery vehicle. It is unclear what Applicant's means by stating the repeated reference of the particle size of the dendrimer by Florence et al. would not have lead one to use dendrimers with a $\log K_{ow}$ exceeding 1. Florence et al. do not teach that certain sized dendrimers have different logKow values. Florence et al. do teach that all of the dendrimers used in the experiments were synthesized as taught on page 254, column 2, and this dendrimer has a $\log K_{ow}$ exceeding 1. Therefore, one of ordinary skill in the art would have used a dendrimer with the same characteristics given Florence et al. teach such dendrimer can efficiently be used as a drug delivery vehicle.

Applicant argues that neither Manoharan I nor Cook et al. provide critical teachings or suggestions that would lead the skilled artisan to adopt ligands with logKow exceeding 1 as opposed to ligands with logKow less than 1. Applicant's

arguments are not convincing. Neither Manoharan I nor Cook et al. were relied upon to teach the advantage lipophilic groups with a logKow value exceeding 1. Manoharan I was relied upon to teach conjugation of lipophilic groups to the 5' or 3' ends enhances the cellular uptake of such molecules and teach such conjugates can be attached to the 5' or 3'ends using linkers such as phosphorodiester. Cook et al. was relied upon to teach methods of increasing the stability of an inhibitory nucleic acid and teach attaching a carbamate cholesterol group increases the stability of said molecules. As stated in the previous Office action and retired herein, it would have been obvious to one of skill in the art to use a known oligonucleotide conjugate, such as a sterol or aromatic group or a cholesteryl carbamate, as taught by Manoharan et al. and Cook et al., to link to a dsRNA taught by Rana. Such oligonucleotide conjugates taught by Manoharan et al. and Cook et al. were known in the art at the time of filing of the instant application to efficiently conjugate to inhibitory molecules and further the field was replete with prior art demonstrating predictable results of increased stability and enhanced uptake of nucleic acid molecules.

Lastly, Applicant argues the Examiner is incorrect in concluding that Monaharan II teaches that "one can synthesize an ideal drug with predictable results" because nothing in Manoharan II would lead one of skill in the art to make the specifically claimed compound. Applicant has misinterpreted Examiner's point. First, the Examiner did not make the statement "one can synthesize an ideal drug with predictable results". The Examiner stated that because the claimed oligonucleotide conjugates were known in the art at the time of the invention of the instantly claimed invention and because

such conjugates were known to efficiently improve the cellular delivery of oligonucleotides and increase their affinity for the target gene as well as increase their resistance to nucleases, it would have been obvious to one of ordinary skilled in the art to use the conjugates taught by Manoharan et al. and Cook et al. with the dsRNA to achieve the predictable result of improvement in cellular delivery of nucleic acids such as dsRNA. Therefore, it would have been obvious to one of ordinary skill in the art to use the known conjugates to improve the cellular delivery of dsRNA.

Thus, the rejection of record is maintained.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-

3111. The examiner can normally be reached Monday thru Thursday between 6 and 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

KC
Examiner Art Unit 1635

/Sean R McGarry/

Primary Examiner, Art Unit 1635